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SYSTEMIC BACITRACIN IN THE TREATMENT OF PROGRESSIVE BACTERIAL SYNERGISTIC GANGRENE*

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IN 1926, THE ETIOLOGY of progressive bacterial synergistic gangrene was first clearly demonstrated by laboratory studies by one of us (F. L. M.) in connection with a case of Dr. George E. Brewer, and was reported in the ANNALS OF SURGERY.[1] It was found that far out in the spreading periphery of the lesion, a micro-aerophilic nonhemolytic streptococcus was present in pure culture and in the gangrenous margin it was associated with a hemolytic *Staphylococcus aureus.* In animals, it was demonstrated that these two organisms together were capable of producing a gangrenous lesion when combined, while neither alone in pure culture was able to produce any significant infection. This was later confirmed in 1931 in a similar fashion by laboratory studies in connection with a case of Dr. Richmond L. Moore's, again published in the ANNALS OF SURGERY.[2] Three more cases were described in 1933 and the differential diagnostic features between this disease and other types of infectious gangrene were described.[3]

The comparative rarity of this disease is probably due to the fact that the organism in the spreading periphery is one of relatively low virulence and the establishment of the infection depends upon the coincident presence of a staphylococcus capable of producing gangrene in tissue already inflamed by the nonhemolytic micro-aerophilic streptococcus. However, the disease is geographically widespread, because typical cases have been reported from North and South America, Europe, Asia and Australia. Well over 100

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cases have been described in the last 25 years and it is now thoroughly established as a clinical entity and should be promptly recognized by every surgeon of experience.

Routine bacteriologic studies have often failed to reveal the essential organisms, because it is necessary to use careful anaerobic cultural methods if the pin point colonies of the micro-aerophilic nonhemolytic streptococcus are to be found. Where a careful search has been made for this organism it has been recovered almost invariably and, unless such studies have been carried out, no one is entitled to question the findings of those careful bacteriologists who have used all of the methods necessary to demonstrate both aerobic and anaerobic bacteria. The cultural characteristics of these organisms have been fully outlined in the reports referred to above.[1, 2]

Certain authors have confused this clinical entity with other destructive lesions of the skin and subcutaneous tissues and in certain articles a heterogeneous mass of data has sometimes been collected under the term, "phagedenic ulcer." This is illustrated in a recent article by Dostrovsky and Sagher[4] in which it is obvious from the clinical course, the illustrations, and the bacteriologic findings that the article presents a wide variety of infections, including, to be sure, some cases of progressive bacterial synergistic gangrene. This is particularly unfortunate, because other authors have been trying to differentiate clearly clinical and bacteriologic entities among the various lesions, which in the past have been called phagedenic ulcers, a term which goes all the way back to Hippocrates and was used by many other authors long before precise bacteriologic methods were available.

It is true that in the early stages of this disease it may not be clearly differentiated from other skin infections or postoperative wound infections, but during the second or third week of its development it takes on certain clinical aspects which are unmistakable.

The chief symptom is the extraordinary pain and tenderness of the lesion. The gross appearance is characteristic. There is an outer zone of erythema varying from 1 to 10 cm. in width; inside of that a raised purple zone, the outer margin of which blends into the erythematous zone, while the inner margin is more sharply defined, crenated in outline, dark purple in color and is firmly adherent to a zone of gangrenous skin which has a typical suede leather, yellowish or brownish-green mottled, coloration and varies in width from 1 to 3 or 4 cm. The inner margin of the gangrenous zone is only slightly undermined, but it gradually melts away as the whole lesion spreads outwardly in all directions. The center of the lesion is a granulating ulcer, the granulations being of shaggy consistency, but as time goes on, this area may become bright red in color and relatively clean. The lesion is essentially a superficial infection and, as it spreads outward, it often leaves behind epithelial remnants of hair follicles or sweat glands which serve as the origin of regenerating epithelium.

The disease often starts in the skin around retention sutures which have been used to close, partially, an operative wound following the drainage of a

peritoneal abscess or an empyema. Very often the deep part of the wound closes while the characteristic gangrenous ulceration continues to spread on the surface. The disease is not always postoperative. Sometimes the lesion slowly develops around a colostomy or an ileostomy or in a trivial superficial accidental wound or in a skin lesion of long standing due to some other cause. Any break in the skin may permit secondary contamination with these organisms and, if they become established in the lesion, they may invade the surrounding tissues and produce the characteristic features of this clinical entity.

When the lesion has developed these characteristic symptoms and signs, there can be little doubt about the diagnosis. Thus, it has been possible to classify in this category many of the cases which have been reported in the literature on the clinical course alone, without the bacterial confirmation of the etiology but, unless the cases fit this clinical picture or unless the bacteriologic findings above mentioned are obtained, gangrenous infections of the skin should not be classified as cases of progressive bacterial synergistic gangrene and should be placed in other categories.

Until 1945 nothing had been found capable of bringing this infection under control except wide surgical excision. It is obvious from the nature of the pathology that the application of any local medication would be of no avail and, although a number of authors have stated that zinc peroxide has been recommended for this condition, such is not the case. Formerly, even excision frequently failed if the margin was not wide enough to remove all of the organisms spreading out from the periphery or if they became established again on the surface of the wound. Zinc peroxide has often been used successfully *after* excision to control any surface contaminants, but it has no place in the treatment of this disease without primary excision.

The sulfonamides have failed to change the course of this disease in any way, but, when penicillin became available, it was, of course, soon applied to this condition. Several favorable reports have appeared. The first included two typical cases reported by Meleney, Friedman and Harvey.[5] These cases responded so rapidly to penicillin that excision of the lesion was obviated. The erythema promptly disappeared, the raised purple zone flattened out and the gangrenous margin separated spontaneously. The defect was then covered with skin grafts. However, a third case of this kind, reported by these authors, which had multiple lesions developing spontaneously from trivial scratches, failed to respond to penicillin and it was demonstrated that one of the secondary contaminants of the *Ps. pyocyanea* group was present and actively produced a penicillinase, thus nullifying the benevolent action of penicillin at the site of the lesion. In this case, wide excision was necessary to control the infection, but the patient died later of pulmonary embolism. This casualty might have been avoided if bacitracin had been available at that time. The curative effect of penicillin in several other typical cases of progressive bacterial synergistic gangrene has been recently reported by Grimshaw and Stent in 1945,[6] by Canton in 1945–46,[7] by Cedarblade and Orr in 1946,[8] and by Clarke in 1947.[9]

Many of the reports of this disease have been simple descriptions of a single case and only very seldom has this clinical entity come into the experience of any individual surgeon more than once. However, a number of authors have attempted to collect all of the previously reported cases and excellent reviews have been made by Stewart-Wallace up to 1935,[10] by Dodd, Heekes and Geiser up to 1939[11] and by Meleney, Friedman and Harvey up to 1944.[5] Not included in the last review is a report by Hillenbrand and Brandt in 1943[12] which includes several cases of this disease mixed with other clinical entities and another authentic case observed by Gurruchaga and Manzoni in 1944.[13] Besides the four reports of cases treated with penicillin mentioned above, other typical cases have recently been described by Bassow in 1945,[14] by Martin and Cadiñanos in 1947,[15] by Cortese in 1947,[16] and by Lyall and Stuart in 1948.[17] This last report is of considerable interest because, while these authors confirm the synergistic etiology of the disease, they believe that *B. proteus* may be the synergist with the micro-aerophilic nonhemolytic streptococcus. In their first case they found these two organisms and failed to find a staphylococcus. Moreover, they were able to produce a lesion in animals when they combined the proteus and the streptococcus, but they could not produce any lesion with either organism in pure culture. While it is possible that in their first case the staphylococcus was masked by the proteus, the animal experiments carry considerable weight.

The present paper is written to record five typical cases of progressive bacterial synergistic gangrene, four of which failed to respond to penicillin but all of which yielded promptly to the systemic administration of bacitracin. In four of these cases we have demonstrated either that the organisms were resistant to penicillin or that there were secondary contaminants capable of producing penicillinase. Certain staphylococci, particularly those that are resistant to penicillin, are often able to produce penicillinase, as are many of the gram-negative aerobic rods and many strains of *Bacillus subtilis,* all of which are common contaminants of any open wound of long standing. It seems likely, therefore, that in the future there will be other cases similar to these that will require bacitracin or some other antibiotic when penicillin has failed, and it seems reasonable on the basis of these cases to recommend bacitracin as the primary treatment of choice.

CASE REPORTS

Case 1.—A. W., age 32 (Patient of F. L. M.; Hosp. No. 890692) was admitted November 17, 1947, and discharged January 14, 1948.

Four months before admission, this patient had been operated upon for fibroids of the uterus in one of the city hospitals. Retention sutures were used to close the abdominal wound, but, about the end of the first week, swelling and redness developed around the lower retention suture and the infection then gradually spread along the whole wound, which became extremely painful as the infection extended in all directions. The involved skin slowly became necrotic, leaving behind a shaggy ulcerated surface. It failed to respond to penicillin, streptomycin and sulfadiazine which were given systemically and to various agents which were used locally. Gradually the lesion took on the typical appearance of progressive bacterial synergistic gangrene. After two months of inexorable

spread, the surgeon in charge attempted to stop the progress of the disease by cutting a trench around it with the electric cautery. The trench was packed with gauze soaked with penicillin solution and for a time the infection seemed to be under control. Small skin grafts taken from the left thigh were applied to the central area, but they failed to take. A secondary closure of the trench was attempted, but infection promptly jumped the trench and spread out into the flanks and down both thighs. Four months after the onset of the infection, the patient was finally seen in consultation and a transfer to the Presbyterian Hospital was arranged (See Figs. 1, 2 and 3).

Physical Examination. The patient was a young colored woman with an extensive lesion involving the lower two-thirds of the abdomen extending out into the flanks on both sides and down both thighs. In the advancing margin on each thigh there was a

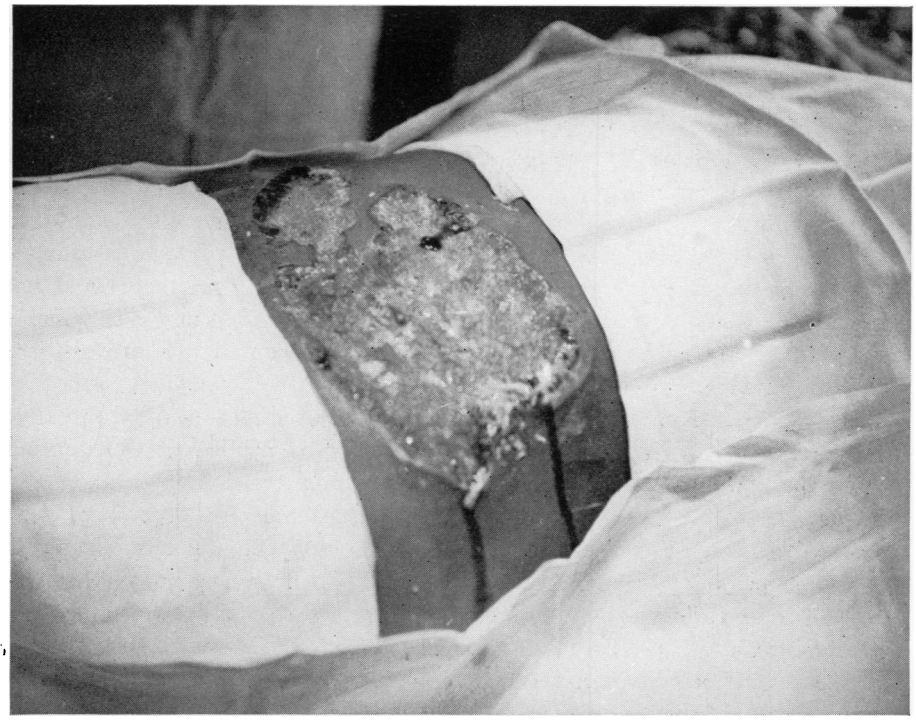

FIG. 1.—Case 1. The extent of the lesion after two months, showing the typical "suede leather" gangrene, the raised purple zone and the erythema around a part of the margin.

crescent-shaped area of suede leather gangrene, 3 to 4 inches long and about an inch wide, densely adherent to the surrounding skin, which was somewhat raised and purple in color. On the side of the skin toward the gangrene there was a sharp line of demarcation, but on the outer side the purple zone faded off into a zone of erythema, varying in width from ½ to 1 inch, but which was rather hard to discern through the pigmented skin. On the upper margin of the lesion on the abdomen, there was a narrower zone of frank gangrene, but a similar raised purple zone and an erythematous zone. The center of the lesion was made up of shaggy granulation tissue with here and there islands and areas of regenerating and degenerating epithelium.

Cultures were taken from various portions of the surface but not from the periphery of the lesion. The cultures were all overgrown with proteus, but, by means of a medium which partially inhibited the growth of this organism, a coagulase positive staphylococcus,

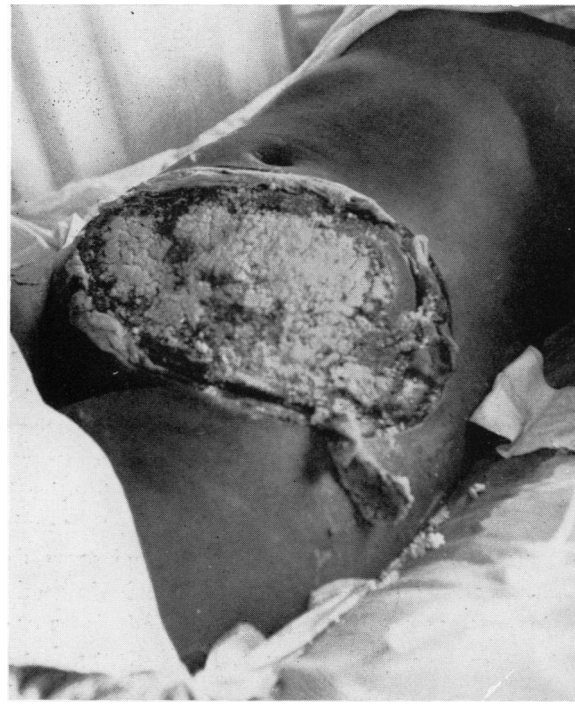

FIG. 2.—Case 1. Appearance of the lesion after two and one-half months. Attempt was made to control the infection by zinc peroxide and by cutting a trench packed with gauze soaked in penicillin.

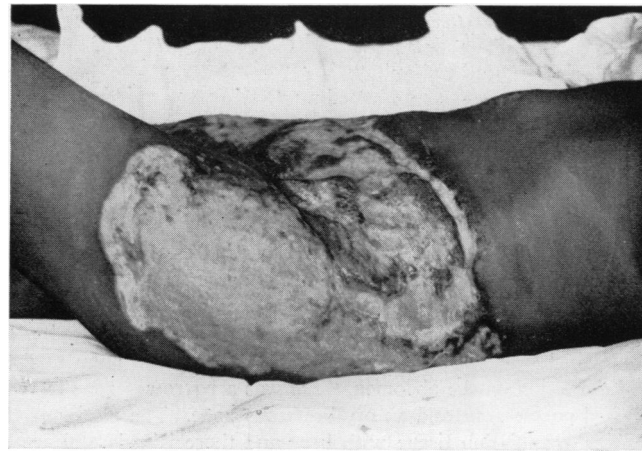

FIG. 3.—Case 1. Appearance of flank and left thigh when first seen by the senior author, four months after onset.

which was resistant to penicillin but susceptible to bacitracin, and a pyocyaneus, were found. Both the staphylococcus and the pyocyaneus demonstrated their ability to produce penicillinase, which offered an explanation for the failure of the infection to respond to penicillin. The micro-aerophilic nonhemolytic streptococcus was not found, as it might have been if cultures had been taken at the spreading periphery of the lesion. This is the first case of typical progressive bacterial synergistic gangrene in which it was impossible for our laboratory to find this essential organism, but the course and the clinical aspects of the case leave no doubt as to the diagnosis.

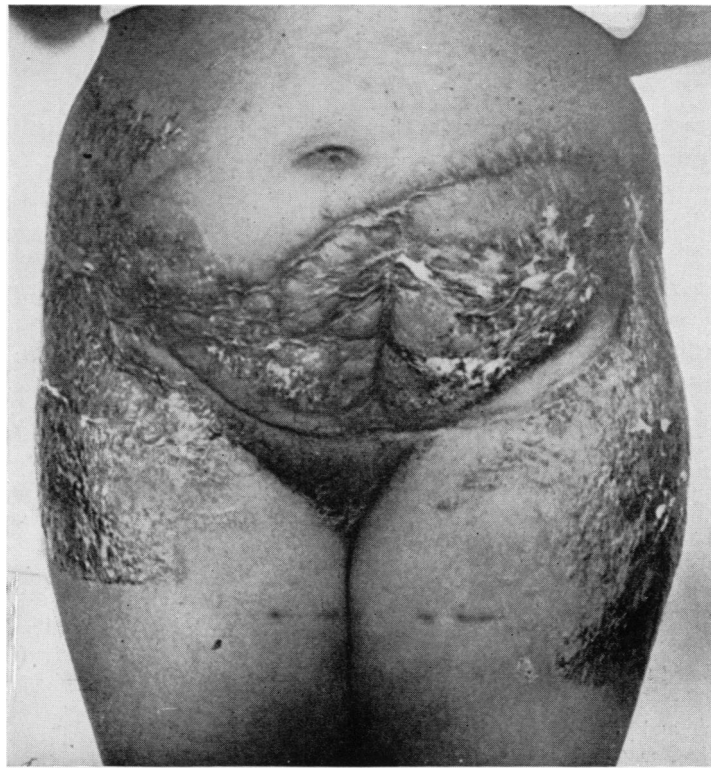

FIG. 4.—Case 1. Complete healing of lesion seven weeks after starting bacitracin.

Course. The patient was given 20,000 units of bacitracin intramuscularly every 6 hours. Bacitracin was also used locally in a concentration of 1,000 units per cc. on a single layer of fine meshed gauze kept moist by a double layer of zinc oxide ointment gauze. There was a dramatic improvement in the patient's general condition as well as in the local lesion in 48 hours. The erythema promptly receded. The purple zone flattened out and the gangrenous skin on the right thigh became loose and detached from the purple zone and it was easily lifted off as a plaque. On the third day, the gangrenous skin on the left thigh was similarly removed without the necessity for cutting. The whole lesion very rapidly took on a benign appearance, the margins flattened down and the exudate became less. Within a week, it was clearly obvious that new epithelium was growing with great rapidity from residual islands all over the surface of the lesion, in spite of the fact that gram-negative rods were present which were not affected by the bacitracin. However, in order to hasten healing by the inhibition of the activity of these organisms,

0.25 per cent of parachlorophenol was added to the bacitracin solution for local application to the surface by means of fine meshed gauze.

After that the whole area rapidly became completely epithelialized. The later stages of epithelialization were hastened by the local application of 2 per cent oxyquiniline in 5 per cent scarlet red ointment. Healing, therefore, did not require either excision or skin grafting. Convalescence was complicated by an intercurrent intestinal infection with *Salmonella montevideo* which caused a diarrhea with high fever and a septicemia, but this halted the healing process only temporarily. Other patients in the ward suffered from this infection at the same time and it was evidently due to food contamination. There was no evidence of toxicity from either the local or the systemic bacitracin which was continued for 30 days for a total dosage of 2,160,000 units systemically and 357,000 units locally (See Fig. 4).

This case clearly demonstrates the efficacy and safety of systemic bacitracin in the treatment of progressive postoperative bacterial synergistic gangrene, obviating the necessity for surgical excision or skin grafting, after the failure of penicillin, streptomycin and sulfadiazine in large doses over a period of four months. Bacitracin was not inhibited by the staphylococcus or the secondary contaminant, *Ps. pyocyaneus,* which were not only resistant to penicillin but which were both capable of producing penicillinase. This result could not have been obtained by the local application of any medication, for it could not hope to reach the spreading border of the lesion. It, therefore, must be assumed that the systemic drug was chiefly responsible for bringing the infection under control.

Case 2.—D. R., age 44 (Patient of F. L. M.; Hosp. No. 904634) was admitted March 30, 1948, and discharged April 21, 1948.

This patient had had chronic ulcerative colitis off and on for a period of 15 years, but this was held under fair control by diet. Five weeks before admission to the hospital, she had a slight abrasion on the front of her right leg. This became infected and an ulcer formed which gradually spread downward toward the ankle, then posteriorly and then up the calf toward the popliteal space, with an advancing zone of erythema and a progressive death of skin. The process advanced insidiously in spite of large doses of penicillin, streptomycin and sulfadiazine and various and sundry local applications, all of which had no effect, but, as the lesions spread outward, there was some evidence of regenerating epithelium in the central portions which were otherwise covered by granulation tissue. The pain had been so great that she had not had a good night's sleep since the onset of the infection.

Physical Examination. The patient was a poorly nourished, thin, anemic woman in great pain and anxiety. The right leg was almost completely surrounded by an extensive ulcer extending from the ankle up to the popliteal space and involving about three-fourths of the circumference of the leg, leaving only a narrow zone of uninvolved skin at the front. Around most of the margin there was a zone of gangrene which was widest on the calf just below the popliteal space. The zone of erythema was of varying width extending well up into the popliteal space where the spread seemed to be most active. The central portion of the lesion was covered with granulation tissue with some irregular islands of regenerating and degenerating epithelium. The whole area was stained irregularly with gentian violet, the last of the ineffective local medications to be applied. Cultures taken from beneath the gangrenous margin revealed the micro-aerophilic nonhemolytic streptococcus and the *Staphylococcus aureus* characteristic of the bacteriology of progressive bacterial synergistic gangrene. The streptococcus was sensitive to both bacitracin and penicillin, while the staphylococcus was sensitive to bacitracin but resistant to penicillin.

Course. The patient was very apprehensive and soon after her admission she began to have a diarrhea which she said indicated a reactivity of the colitis. She was given bacitracin in a dosage of 24,500 units every 6 hours intramuscularly and because of the diarrhea 5,000 units of bacitracin were administered by mouth four times a day. Bacitracin was also used locally on fine meshed gauze in a concentration of 500 units per cc. This was covered by a double layer of gauze impregnated with zinc oxide ointment to keep the dressing moist. Improvement was evident within 48 hours. The erythema faded rapidly and the raised purple zone flattened out and its color improved. The gangrenous skin began to separate from the purple zone and from the tissue beneath it. The islands of epithelium at the center began to regenerate at their margins. In a week's time, all of the dead skin had separated and the area was half covered with new skin. During the first week, the colitis subsided completely. After two weeks, the epithelium had covered all but an area two inches in diameter at the upper part of the calf. Final epithelialization was complete when the patient went home on the twenty-second day. The urine showed a transient albuminuria and cylindruria, but blood studies showed no elevation of the nonprotein nitrogen or the urea nitrogen. Phenolsulphonphthalein elimination was 80 per cent in two hours at the end of treatment. Systemic bacitracin was continued for 18 days for a total of 1,715,000 units; 78,000 units were used locally and 415,000 were given by mouth. (It is not absorbed to any great extent from the gastro-intestinal tract, where it is retained and inhibits the growth of susceptible organisms.)

This case illustrates the prompt response to systemic and local bacitracin of a typical case of progressive bacterial synergistic gangrene resulting from the establishment of the characteristic bacterial species in an abraded wound. Penicillin, streptomycin and sulfadiazine had all failed to control the infection and, because of its nature, we must assume that it was the systemic rather than the local bacitracin which halted the progress of the infection. Possibly the systemic as well as the mouth medication helped to control the associated colitis.

Case 3.—F. B., age 57 (Patient of F. L. M.; Hosp. No. 749989) was admitted April 20, 1948, and discharged July 1, 1948.

The patient had suffered from mycosis fungoides for a number of years with lesions all over his body, particularly on the feet. The involved areas usually developed slowly with localized swelling and redness and then dissolution of the overlying skin would follow with or without blistering. The diagnosis had been repeatedly confirmed by biopsy. These lesions frequently became infected, but this feature was of minor importance and was generally controlled by simple local medication. On one of these occasions, he was given penicillin by mouth and penicillin ointment locally, but it had to be discontinued because of penicillin allergy. About two months before admission to the hospital, however, an area of gangrene developed on the side of the right foot and the surrounding tissue became acutely inflamed and swollen. This area slowly enlarged and gradually took on the characteristic appearance of progressive bacterial synergistic gangrene with a zone of densely adherent necrotic skin surrounded by a raised purple zone with a surrounding fiery red erythema. The whole area became extremely tender and painful and the patient's attending dermatologist then referred him to the hospital for the control of the infection.

Physical Examination. The patient was well developed and nourished, but in considerable pain from the lesion on his foot, which extended from the bases of the toes up to the front and outer side of the ankle. There were two areas of adherent suede leather gangrene connected by a narrow strip of ulcerated skin with a raised purplish margin (Fig. 5). The whole area was swollen and surrounded by a cellulitis, the erythema extending in all directions, particularly toward the inner side of the foot. On the sole were several areas of mycosis fungoides not involved in the gangrenous process. Cultures

from the lesion revealed the micro-aerophilic nonhemolytic streptococcus and the coagulase positive *Staphylococcus aureus,* both susceptible to penicillin and bacitracin, as well as *Ps. pyocyaneus.*

Course. The patient was given bacitracin in a dosage of 19,000 units every 6 hours and the local lesion was dressed with a carbowax (water soluble) ointment containing 500 units of bacitracin per gram with a quarter of one per cent parachlorophenol to take care of the pyocyaneus. Improvement was striking. The cellulitis and erythema subsided promptly. The dead skin separated at the margins and after three days it was possible to peel it off from the underlying tissues. New skin then began to grow in from the margins and from residual islands of epithelium. The cocci disappeared promptly, but the pyocyaneus persisted for some time in the culture. Healing then took place slowly. The pyocyaneus gradually disappeared from the wound and the lesions of mycosis fungoides responded to small repeated doses of roentgen radiation.

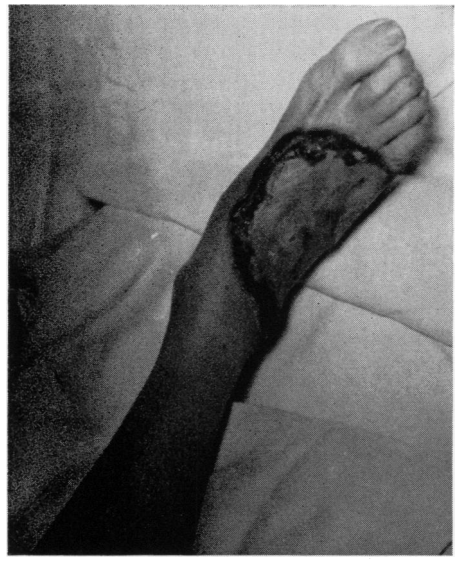

FIG. 5.—Case 3. Appearance of the lesion when first seen by the senior author, showing the "suede leather" gangrene, the raised purple zone and the erythema.

Urinalysis was normal and the N. P. N. was 26 mg. per 100 cc. before starting bacitracin, but gradually albumin, casts and cellular elements appeared in the urine. The N. P. N. rose to 43 mg. per 100 cc. and the P. S. P. fell from 70 per cent to 35 per cent. It did not seem necessary to stop treatment, but the lot was changed on the eleventh day from No. 480120 to No. 480210. On the next day, a rash appeared across the shoulders and gradually spread all over the back and chest with a few areas on the arms. Therefore, the infection having been controlled, it was decided on the twelfth day to stop the systemic bacitracin but continue it locally. The rash slowly subsided following benadryl and pyribenzamine. The N. P. N. promptly returned to normal and the P. S. P. rose again. A later study of toxicity of various lots of bacitracin showed that the ones used in this case were among the most toxic, but they were clinically effective and the evidences of kidney irritation or damage were promptly reversible. (Considerably less toxic lots are now available.)

This case illustrates the development of progressive bacterial synergistic gangrene following the contamination of the lesions of mycosis fungoides with the essential organisms of this synergistic infection. After other treatment had failed, the infection promptly responded to bacitracin and, although this manifested some side effects of nephrotoxicity, they were transient and did not interfere with the clinical effectiveness of the drug.

Case 4.—L. H., age 42, a patient of P. S., Illinois Masonic Hospital No. 99355, was admitted January 19, 1948, and discharged April 27, 1948.

This patient had been suffering for six months with a bloody diarrhea which had resulted in a weight loss of 50 pounds and a progressive cachexia and anemia. Colonic roentgen rays showed a typical advanced ulcerative colitis. No amebas were found in the

stools. Daily spikes of fever ranged from 100° to 102°. She made no response to a strict dietary regimen over a period of one month in the hospital and ran a progressively downhill course. Then a double-barrelled ileostomy was performed and resulted in slight improvement in her general condition, but a profuse muco-purulent rectal discharge continued and the patient developed a progressive hypoproteinemia which could not be controlled by repeated blood and plasma transfusions and various intravenous and per os protein hydrolysates. Her weight remained around 110 and her legs became progressively edematous. The skin about the ileostomy remained in good condition for several weeks and then began to show small superficial breaks in the surface, which soon showed signs of infection. This resisted all efforts to control it. Finally, 8 weeks after the ileostomy, an infection started on one side of the stomata with swelling and redness and discoloration of the skin. This went on rapidly to a spreading necrosis with all of the characteristic features of progressive bacterial synergistic gangrene, extending outward from the stomata in all directions. Almost simultaneously, similar gangrenous areas developed in the right flank and on the right leg just above the ankle. The lesions were characterized by extreme pain and tenderness and rapid spread and the patient's morale began to fail rapidly. Penicillin in large doses, sulfadiazine, and streptomycin were tried systemically to no avail, while zinc peroxide, tyrothrycin, penicillin and azochloramide were used locally without benefit. Finally, the surgeon in charge called for bacitracin.

Physical Examination. The lesions showed all of the typical features of progressive bacterial synergistic gangrene. Around the ileostomy stomata the lesion measured 4 by 5 inches, in the flank 2 by 3 inches and on the leg 5 by 6 inches. In each area there was a central ulceration with boggy granulations covered by a purulent exudate. Around this was a zone of yellowish black gangrenous skin surrounded in turn by a raised purple zone and beyond that an erythema of variable width. Cultures from the ulcerated areas revealed a coagulase positive *Staphylococcus aureus,* susceptible to bacitracin but resistant to penicillin. The laboratory reported that the anaerobic cultures showed no growth, but this must have been an error because the staphylococcus, if present aerobically, would certainly have grown on the anaerobic plate or in anaerobic broth and might well have masked the smaller colonies or the slower growth of the micro-aerophilic nonhemolytic streptococcus.

Course. When bacitracin was made available, the patient received 24,500 units intramuscularly every 6 hours and this was continued for 11 days, for a total of 1,078,000 units. The progress of the infection came to a standstill in 48 hours. The gangrenous skin soon began to separate spontaneously, the raised purple zone flattened out and the erythema progressively diminished. The exudate became scanty and the granulations took on a firm consistency and a bright red color. The areas on the abdomen and flank were covered with "pinch" grafts on the twelfth day and the ankle on the fourteenth. These grafts rapidly fused and covered the areas with new skin.

After stopping the systemic bacitracin, the rectal purulent discharge, which had markedly diminished during treatment, recurred. Bacitracin was then introduced into the distal ileostomy stoma in solution form in a dosage of 5,000 units once a day. The purulent character and the quantity rapidly diminished and the patient's general condition and morale steadily improved.

This case illustrates the development of the typical lesion of progressive bacterial synergistic gangrene around an ileostomy in a case of chronic ulcerative colitis and two simultaneous similar lesions on other areas of the body, which failed to respond to penicillin in large doses, sulfadiazine and streptomycin, but which were controlled within 48 hours by systemic bacitracin. The gangrenous skin separated spontaneously and the resulting ulcer rapidly prepared itself to accept skin grafts, which readily took hold and covered the

defect. At the same time, the ulcerative colitis cleared rapidly, first under the systemic treatment and again under the local administration of bacitracin.

Case 5.—M. B., age 34, a patient of R. S. M. at North Country Community Hospital, Glen Cove, L. I., No. 64452, was admitted November 15, 1948, and discharged December 13, 1948.

The patient was admitted at term in mild labor of one hour's duration. There had been a long record of infertility. Her antepartum course had been relatively uneventful.

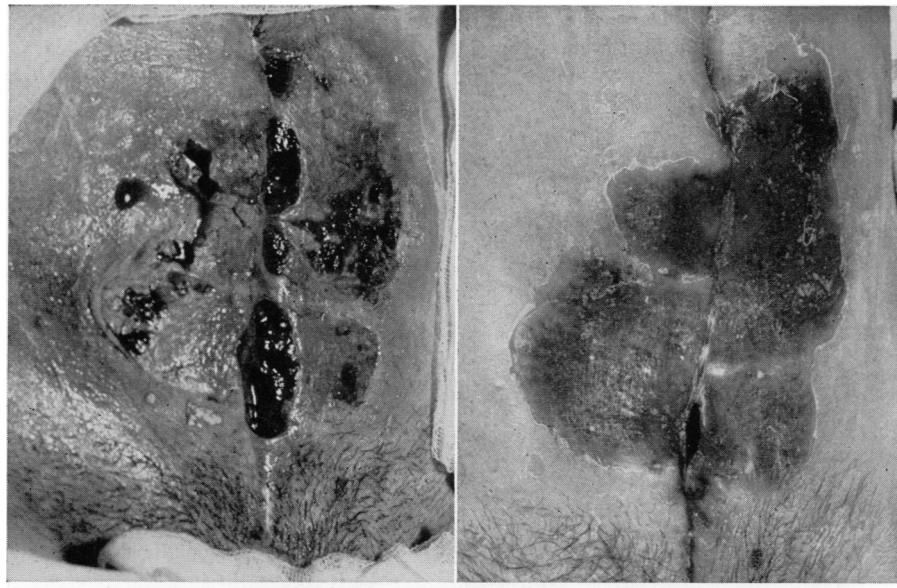

FIG. 6 FIG. 7

FIG. 6.—Case 5. Appearance of the lesion on its ninth day, just after starting bacitracin, showing the early characteristic features of the disease, a carbuncular appearance with a raised bluish-purple zone of necrobiotic tissue.

FIG. 7.—Case 5. Appearance of the lesion ten days after starting bacitracin, showing complete resolution of the process without any death of the skin and with rapid healing.

After six hours of moderate contractions, the membranes ruptured and good hard labor ensued. After 13 hours, the cervix was three fingers dilated. The following three hours of strong uterine contraction produced no progress. The fetal heart became accelerated and, in view of the low index of fertility, a cesarean section was deemed advisable. The patient was given 60,000 units of penicillin in distilled water intramuscularly prophylactically. A cesarean section was performed without difficulty through a low midline abdominal incision and a transverse low flap uterine incision. Two grams of sulfanilamide crystals were sprinkled underneath the bladder flap after closing the uterine incision. The abdomen was closed in layers with catgut. Four silk stay sutures were inserted and threaded through rubber tubing.

Following the operation, 40,000 units of penicillin were administered intramuscularly every 3 hours for 6 days; and 7 hours after the operation, 1 Gm. of sulfadiazine, in combination with 2 Gm. of soda bicarbonate, was given orally every 4 hours for 3 days. On the second postoperative day, the patient was allowed out of bed. Her postoperative course continued satisfactorily until the eighth postoperative day, at which time exam-

ination of the abdominal wound revealed small vesicles lateral to the ends of each piece of rubber tubing, underneath the stay sutures, such as one would see in a second degree burn. It was considered at this time that the patient was probably sensitive to the rubber and was having an allergic skin reaction. The tubing was cut out, leaving the stay sutures in place. Twenty-four hours later the vesicular areas had spread so as to almost join each other in the midline and there was some redness along the wound edge, indicative of a secondary infection. Penicillin was resumed on the twelfth postoperative day. Cultures of the wound taken at this time revealed *E. coli* when read 48 hours later. On this account, penicillin was stopped and streptomycin was given in combination with sulfadiazine, but they had no effect. The entire wound became inflamed. The wound margins separated for a width of about 2 cm. and a depth of 1 to 1½ cm. All along the wound surface there was a purulent exudate and a dusky swelling appeared around the retention sutures, especially at the upper part of the wound on the left side. It was obvious that this represented the earliest changes seen previously in typical cases of progressive bacterial synergistic gangrene and it became of considerable importance to stop the process before it could result in extensive death of skin. Penicillin and sulfadiazine both had failed as prophylactics and penicillin, streptomycin and sulfadiazine had failed to stop the infection after its onset. Additional cultures confirmed the diagnosis by revealing a hemolytic *Staphylococcus aureus,* resistant to penicillin but susceptible to bacitracin, and a micro-aerophilic nonhemolytic streptococcus. *Escherichia coli* and aerobacter were also present. These species are both capable of producing penicillinase, although this effect was not demonstrated for these organisms *in vitro* (See Fig. 6).

Course. On the sixteenth postoperative day and on the eighth day of the infection the stay sutures were removed and bacitracin was given in a dosage of 10,000 units every 6 hours intramuscularly. It was applied locally on wet compresses in a concentration of 1,000 units per cc. The dressings were kept moist by the application of zinc oxide ointment gauze. The photographs taken on the seventeenth postoperative day illustrate the status of the wound 24 hours after medication was instituted, at which time there was already some improvement. Additional photographs taken at the end of ten days revealed the wound closed except for a small area measuring about ¼ cm. (See Fig. 7).

During the administration of the bacitracin, daily checks were made on the patient's urine, nonprotein nitrogen and phenolsulphonphthalein tests. The patient developed three plus albumin in her urine on the fourth day following administration of bacitracin, but this gradually decreased during treatment. Urinalysis and blood chemistry taken after the patient's discharge from the hospital were normal.

This case illustrates the development of progressive bacterial synergistic gangrene in a cesarean section wound made after the rupture of the membranes, the organisms probably coming from the vagina. It developed in spite of the prophylactic use of penicillin and of sulfadiazine both locally and systemically, probably because of the associated Gram negative rods. After its development, it failed to respond to penicillin, sulfadiazine and streptomycin. Its nature was recognized early before there was extensive death of skin. Its progress was promptly arrested by the systemic administration of bacitracin. Surgery was obviated and rapid resolution of the process resulted.

COMMENT

The five cases included in this report all showed the characteristic clinical features of progressive bacterial synergistic gangrene. In two of these cases, the micro-aerophilic nonhemolytic streptococcus was not found, but we believe

this was due to the fact that no cultures were taken from the spreading zone of erythema and this organism was probably overgrown by secondary contaminants in the area of gangrene and ulceration. The failure to find this organism does not, therefore, rule out the diagnosis.

Only two of these five cases, the first and the last, were postoperative infections in the usual sense. In Case 4 the lesion developed around an ileostomy eight weeks after operation while two other lesions developed away from the operative site at the same time. Case 2 produced the lesion in a simple abrasion, while in Case 3 the disease followed the contamination of an area of mycosis fungoides. For this reason, the authors feel that the name "progressive bacterial synergistic gangrene" should be retained and used for this clinical entity, but that the word "postoperative" should only be added in those cases in which it develops within the first two or three weeks after operation in the true sense.

Four of these cases failed to respond to penicillin and it was not used in the other case because it had been previously demonstrated that the patient was allergic to penicillin. The failure of penicillin can probably be explained either by the fact that the organisms present were resistant or were capable of producing penicillinase. All of these cases responded promptly to bacitracin and the nature of the infection makes it certain that the systemic administration of bacitracin rather than its local use was largely responsible for this control. In each case the staphylococcus and, where it was found, the microaerophilic nonhemolytic streptococcus were susceptible to bacitracin. It would seem, therefore, that bacitracin rather than penicillin is, at present, the treatment of choice in this disease.

In all of these cases, surgical excision was obviated and, if other similar cases respond in the same way, we believe that excision either with the knife or with the cautery is no longer indicated nor should any attempt be made to stop the infection by cutting a trench around it. In only one of these cases was it necessary to cover over the defect with skin grafts, because in all of the other instances the defect was restored by the growth of epithelium from the residual islands that had been left in the outward spread of the gangrenous process.

In only one of these cases was there any evidence of toxicity from the drug and this was only of moderate severity and short duration and did not interfere with the curative effect of the drug. It was later found that the lots that were used in this particular case were both of relatively high toxicity when compared with the lots used in the other cases and with the product that is now available for systemic use.

The last case demonstrates that this disease can be diagnosed in its early stages both by the characteristic clinical features and by bacteriologic studies. Certainly, as soon as it has formed its characteristic zones by the end of the third or fourth week of its course, it should be recognized by everyone and the proper treatment should be administered. Bacitracin should be started in a dosage of 400 units per kilogram of body weight every six to eight hours.

The urine should be examined every day for albumin, casts, white cells, red cells and epithelial cells and the B. U. N. or N. P. N. should be taken every third day. The presence of albumin or casts in the urine does not require a termination of treatment unless they should reach serious proportions, because it may be expected that they will diminish during the course of treatment or immediately after its termination.

SUMMARY

Five more cases of progressive bacterial synergistic gangrene have been presented herewith, all of which responded promptly to systemic bacitracin after they had failed to respond to other methods of treatment. Four of these had had penicillin without benefit. In the other case, penicillin had not been used because of the previous demonstration of an allergic response.

This series of cases illustrates the disease from its earliest development, when it was recognized at an early stage before extensive destruction of skin, to a very late stage in which, after four months, it had involved all of the lower abdomen, the flanks and the upper portions of the thighs.

All of these cases showed the typical clinical symptoms of progressive bacterial synergistic gangrene and the essential organisms were found in three. In the other two cases, the micro-aerophilic nonhemolytic streptococcus escaped recovery, probably due to the overgrowth of secondary contaminants.

These cases clearly indicate that systemic bacitracin is today the treatment of choice for this clinical entity.

The authors appreciate the careful bacteriologic studies made by Miss Balbina Johnson in connection with Cases 1, 2, 3 and 5.

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